

**SICKLE CELL DISEASE IN CHILDREN AND ADOLESCENTS:
DIAGNOSIS, GUIDELINES FOR COMPREHENSIVE CARE, AND CARE PATHS AND
PROTOCOLS FOR MANAGEMENT OF ACUTE AND CHRONIC COMPLICATIONS***

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**OPERATIONAL & SERVICE GUIDELINES
SICKLE CELL DISEASE**

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INTRODUCTION

Much progress has been made during the past 20 years in the treatment of sickle cell disease. Identification of most affected infants by neonatal screening provides opportunities for educational and medical interventions that significantly reduce morbidity and mortality during childhood and adolescence. Comprehensive medical care includes extensive health maintenance with appropriate prophylactic measures, parental education, psychosocial support, and periodic medical assessment with monitoring for the development of chronic organ damage. Appropriate care also provides for the management of acute illness in a setting where knowledge and perspective about sickle cell disease is available and where physicians have ready access to baseline information about the patient, including results of previous physical examinations, laboratory work, and radiographs. Because acute illness in patients with sickle cell disease can prove rapidly life threatening, it is essential that patients have unimpeded access to providers who have the expertise necessary to quickly recognize and treat potentially catastrophic signs and symptoms. Such care not only reduces morbidity and mortality, but it also may reduce medical costs by preventing some manifestations of the disease and by limiting the severity or sequelae of others. Many acute complications can be managed safely on an outpatient basis, thus reducing the need for hospitalization.

This manual provides information about the diagnosis of sickle cell disease, an overview of comprehensive care, and clinical care paths and protocols for the management of some of the more common acute and chronic complications. The manual originally was developed in 1996 by the staff of the Colorado Sickle Cell Treatment and Research Center, University of Colorado School of Medicine and The Children's Hospital, Denver, CO. Subsequently, it has been revised and expanded annually, most recently by its current authors, pediatricians and hematologists from Arizona, Colorado, Georgia, Missouri, New Mexico, Tennessee, Texas, and Utah who met in November, 2001. Thus, it represents a broad consensus of providers with expertise in sickle cell disease. It is hoped that these guidelines will improve the consistency and quality of care, but the authors recognize that adherence to them does not assure a successful medical outcome and that deviations from them will be appropriate in individual cases. The guidelines are not intended to replace a physician's best medical judgment, nor should they be used as a substitute for hands-on care by providers with experience and expertise in the management of sickle cell disease.

The current revision of the manual was supported in part by a contract from the Genetic Services Branch, Maternal and Child Health Bureau, HRSA. The manual's authors encourage the widespread reproduction and distribution of these materials for any educational and/or patient care related purpose and ask only that the source of the materials be acknowledged. Individual institutions may wish to adopt some or all of the clinical care paths and protocols (with or without modification) for routine use in their outpatient clinics and inpatient units. To facilitate dissemination of this material, the manual is now available on the websites of the Mountain States Genetics Network (www.mostgene.org), the Texas Department of Health (www.tdh.state.tx.us/newborn/newborn.htm) and the Georgia Comprehensive Sickle Cell Center (www.scinfo.org). It is expected that this manual will continue to undergo periodic review with revisions posted on these websites. Its authors welcome comments and suggestions for improvement.

PRINCIPLES OF CARE FOR CHILDREN AND ADOLESCENTS WITH SICKLE CELL DISEASE

Sickle cell disease is a complex genetic disorder with multi-system manifestations that requires specialized comprehensive care to achieve an optimal outcome. Comprehensive medical care

includes ongoing patient and family education, periodic comprehensive evaluations and other disease-specific health maintenance services, timely and appropriate treatment of acute illness, and genetic counseling.

In addition to medical treatment, the management of sickle cell disease requires sensitivity to important psychosocial implications of the disease and services to address them. Barriers to appropriate health care include inadequate insurance coverage, transportation, and/or access to health care providers with expertise in the management of sickle cell disease. Important stresses that often affect a family's ability to cope with sickle cell disease include the economic and educational consequences of time lost from work and school and the impact of chronic illness on normal family functioning, including adjustment issues for non-affected siblings. Families live daily with the knowledge that unpredictable acute illnesses will interrupt daily life, and there are often feelings of powerlessness, frustration, and even anger. A general lack of community awareness about sickle cell disease and fear of stigmatization may limit the support available from extended family, friends, and the community at large. Prior experience with health care providers who lack knowledge, sensitivity, and compassion may contribute to delays in seeking appropriate health care and may engender adversarial relationships between families and providers. Failure to appreciate ethnic and cultural differences between providers and patients and families may also contribute to misunderstanding and lack of trust. Thus, it is imperative that providers take time to listen to the concerns of patients and families, that they be sensitive to psychosocial as well as medical needs, and that they assist families in accessing available resources as needed.

The federal Healthy People 2010 Objectives include six measures for Children with Special Health Care Needs.* These provide guiding principles for the care of CRS Program enrolled Members with sickle cell disease.

1. All members with sickle cell disease will receive regular and ongoing comprehensive care within a medical home.

Optimal care requires the active involvement of professionals in pediatrics and hematology, nursing, social work, psychology, genetics, education, and counseling. The services they provide need to be coordinated through an appropriate medical home. For many patients, the medical home will be a multi-disciplinary sickle cell clinic that coordinates all aspects of comprehensive care in collaboration with the member's primary care physician or that provides specialty and primary care in one setting. In other cases, the medical home may be provided by a knowledgeable primary care provider from whom the patient receives day-to-day care, with periodic referrals to sickle cell specialists for comprehensive evaluations and for the management and treatment of severe, life-threatening complications. The location of the medical home and extent to which care is provided by the primary care provider versus the multi-disciplinary sickle cell clinic will vary among patients and communities and will depend in part on the expertise of the primary care provider, access to a multi-disciplinary sickle cell clinic, family preference, and the frequency and severity of disease manifestations. Good communication among the family, primary care providers, and subspecialists is essential to provide coordinated care and to establish and maintain trust.

2. All families of Members with sickle cell disease should have adequate private and/or public insurance to pay for the services they need.

Almost every member in the U.S. with sickle cell disease is eligible for health care coverage by commercial insurance, Medicaid, Medicare, SSI, or the Children's Health Insurance Plan (CHIP). It is imperative that providers assist families and patients to obtain and maintain adequate insurance coverage. For patients insured by managed care plans, ongoing access

to providers with expertise in sickle cell disease may require advocacy by primary care providers and anticipation of payer requirements for prior authorization for specialty services.

3. All members with sickle cell disease will be screened early and continuously for special health care needs.

Individuals with sickle cell disease require ongoing screening for a variety of disease-related problems. All patients with sickle cell disease should have regularly scheduled comprehensive medical evaluations to review previous disease manifestations, document important baseline physical findings and laboratory values, monitor growth and development, and screen for signs of chronic organ damage. Comprehensive evaluations also provide an ideal setting for providing age-appropriate family and patient education and for evaluating and addressing psychosocial issues.

4. Services for member's with sickle cell disease and their families should be organized in ways that families can use them easily.

Important health and other services may be available but difficult to access because of problems with transportation or parking or a lack of insurance coverage or prior authorization from managed care plans. Access to multidisciplinary comprehensive evaluations can be facilitated by the provision of outreach clinics in communities distant from tertiary care centers. Because acute illness can prove rapidly life threatening, it is imperative that every member with sickle cell disease have a plan for around-the-clock access to a medical facility where knowledge and perspective about sickle cell disease is available, where evaluation and treatment can be promptly delivered, and where providers have access to baseline information about the patient. Other important services include social services, neurocognitive evaluations, and educational and vocational planning and counseling - all of which require communication and coordination among providers, educators, patients, and families. In many communities, patient and family support groups and other valuable supportive, educational, and counseling services are organized and provided by community-based groups, such as local chapters of the Sickle Cell Disease Association of America.

5. Families of members with sickle cell disease will participate in health care decision-making at all levels and will be satisfied with the services they receive.

Parents are ultimately responsible for decisions about their children. In order for parents to participate in decisions regarding their children's health care, they must receive accurate and ongoing education about the disease and about a variety of treatment options. Education should be provided in an open, non-judgmental, and mutually respectful environment. Providers should recognize that personal and cultural beliefs about illness and existing stresses and support systems may greatly impact the family's ability to cope with sickle cell disease and may appropriately influence their decisions. Patients and families should be encouraged to provide feedback about the care they receive and suggestions to improve it.

6. All members with sickle cell disease will receive the services necessary to make appropriate transitions to all aspects of adult life, including adult health care, work, and independence.

The families of members with sickle cell disease should be encouraged to set appropriate goals for their children and to develop realistic strategies to achieve those goals. School personnel must be educated about sickle cell disease and encouraged to accommodate repeated and often unpredictable absences. During middle childhood and adolescence,

education about sickle cell disease is increasingly directed towards the patient, as well as the family, with the expectation that adolescents will be knowledgeable about their disease and its management. Counseling about higher education and vocational choices should be realistic but avoid underestimating the patient's potential. The transition from pediatric to adult health care providers and institutions can be traumatic and requires prior discussion, preparation, and planning. The current shortage of health care providers with interest and expertise in the treatment of adults with sickle cell disease is a major problem that must be addressed.

* A National Agenda for Children with Special Health Care Needs. Measuring Success for Healthy People 2010: A working document. Material and Child Health Bureau, HRSA, September, 1999.

DIAGNOSTIC TESTING COMMON SICKLE CELL SYNDROMES¹

Syndrome	Neonatal Screening ²	Hemoglobin Separation by age 6 weeks ²	Hemoglobin Separation in Older Members (≤ 5 yr)				
			Hb A (%)	Hb S (%)	Hb F (%)	Hb A ₂ (%)	Hb C (%)
Sickle cell anemia (HbSS)	FS	FS	0	75-95	2-25 ⁴	<3.5	0
Sickle β ⁰ -thalassemia ¹	FS	FS	0	80-92	2-15	3.5-7.0	0
Sickle-hemoglobin C disease (Hb SC)	FSC	FSC	0	45-50	1-5	NA ⁵	45-50
Sickle β ⁺ -thalassemia ¹	FSA or FS ³	FSA	5-30	65-90	2-10	3.5-6.0	0
Sickle cell trait	FAS	FAS	50-60	35-45	<2	<3.5	0
Normal	FA	FA or AF	95-98	0	<2	<3.5	0

* Table shows results of hemoglobin separation tests (i.e., hemoglobin electrophoresis, isoelectric focusing and/or HPLC). In selected cases, DNA analysis or testing of parents may be helpful.

- 1 β⁰ indicates thalassemia mutation with absent production of β-globin (i.e. no Hb A); β⁺ indicates thalassemia mutation with reduced (but not absent) production of β-globin
- 2 Hemoglobins reported in order of quantity (e.g., FSA=F>S>A); F, fetal hemoglobin; S, sickle hemoglobin; C, hemoglobin C; A, hemoglobin A. Abnormal results require confirmation with Hb electrophoresis, isoelectric focusing, HPLC, and/or DNA studies (see p. 7).
- 3 Quantity of Hb A at birth sometimes insufficient for detection.

- 4 Hb F levels in rare cases of Hb SS may be high enough to cause confusion with Hb S-pancellular Hereditary Persistence of Fetal Hemoglobin (S-HPFH), a benign disorder not usually associated with significant anemia or vaso-occlusion. In such cases, family studies and laboratory tests to evaluate the distribution of Hb F among red cells may be helpful.
- 5 Quantity of Hb A₂ cannot be measured by electrophoresis in presence of Hb C

NEWBORN SCREENING FOLLOW-UP GUIDELINES¹

Follow-up of Infants with Probable Hemoglobin Disease (i.e. newborn screening results FS, FSC, FSA, FC, FE, FU, F Other, F only, etc.²)

1. The newborn screening laboratory reports positive results promptly to the hospital, sample submitter, and/or to the Newborn Screening Program follow-up coordinator (varies by state). The laboratory or follow-up coordinator (depending on the state) notifies the primary care physician and/or the parents by telephone, FAX, or certified mail of the infant's test results. Whenever possible, contact with the family will be accomplished within 2-3 weeks.
2. The primary care physician or follow-up coordinator will arrange for confirmatory testing (hemoglobin separation by electrophoresis, isoelectric focusing and, and/or HPLC or DNA analysis) in an appropriate laboratory by two months of age, unless the diagnosis has already been confirmed. Testing of parents or DNA analysis may help establish the correct diagnosis in some infants. Consultation with a pediatric hematologist is strongly encouraged.
3. Parents will be notified promptly when a clinically significant hemoglobin disorder has been confirmed. Infants with confirmed sickle cell anemia or sickle β^0 -thalassemia (or with screening results FS not yet confirmed) should be started on prophylactic penicillin (VK 125 mg po bid)³ by 2-3 months of age. Education and written information about the disorder and its treatment and a medical referral to a physician knowledgeable about sickle cell disease (ideally a pediatric hematologist and/or sickle cell clinic) will be provided. Early education about sickle cell disease should emphasize the importance of prompt medical evaluation for fever and for signs and/or symptoms of splenic sequestration. Genetic counseling should be provided (see p. 10).
4. As part of appropriate education, the role of testing parents, siblings, or other family members should be discussed.
5. If the family declines follow-up and confirmatory testing, all follow-up attempts will be thoroughly documented. It may be appropriate to notify Member Protective Services in some instances.

Follow-up of Infants with Probable Hemoglobin Trait (i.e., newborn screening results FAS, FAC, FAE, FAU, FA Other, etc.²) (does not include Hb Bart's)

1. The newborn screening laboratory reports screening results to the hospital, sample submitter, and/or to the Newborn Screening Program follow-up coordinator (depending on the state) within two to three weeks of the screening test.
2. The primary care physician or follow-up coordinator (depending on the state) will contact the parents to recommend confirmatory testing (hemoglobin separation by electrophoresis, isoelectric focusing, and/or HPLC) in an appropriate laboratory by 2-3 months-of-age, unless this has already been accomplished with routine neonatal screening samples (varies by state). As part of appropriate education, the role of testing parents and other family members should be discussed.
3. Education and written materials about the hemoglobin trait and its genetics should be provided to the family when a hemoglobin trait has been confirmed. Education should emphasize the lack of illness associated with these genetic carrier conditions and their potential genetic implications (see p. 10).
4. If the family declines follow-up and confirmatory testing, the case will be closed.

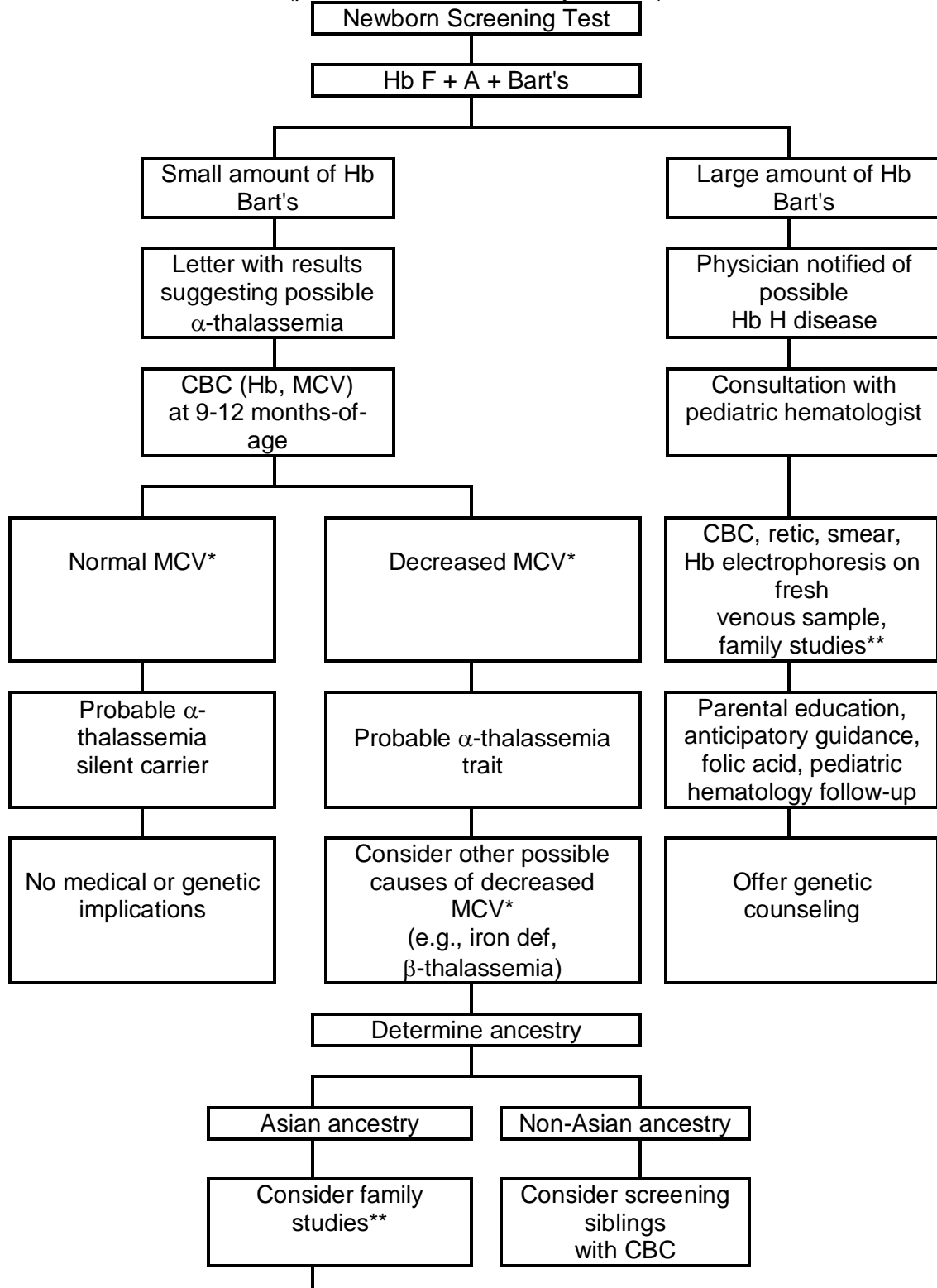
¹ Modified from Newborn Screening Practitioner's Manual, 2nd edition, Mountain States Regional Genetics Services Network, 1996, p. 35.

² Hemoglobins (Hb or Hgb) are reported in order of quantity (e.g., FSA = F>S>A). F=fetal Hb, A=adult Hb, S=sickle Hb; C=Hb C, E=Hb E; U (Other)=unidentified or other Hb (includes Hb D, G, and others)

³ Tablets have a longer shelf life than suspension, which must be reconstituted with water, kept refrigerated, and expires in 14 days.

Follow-up Procedures for Infants with Hemoglobin Bart's on Neonatal Screen

(possible α -thalassemia syndrome)



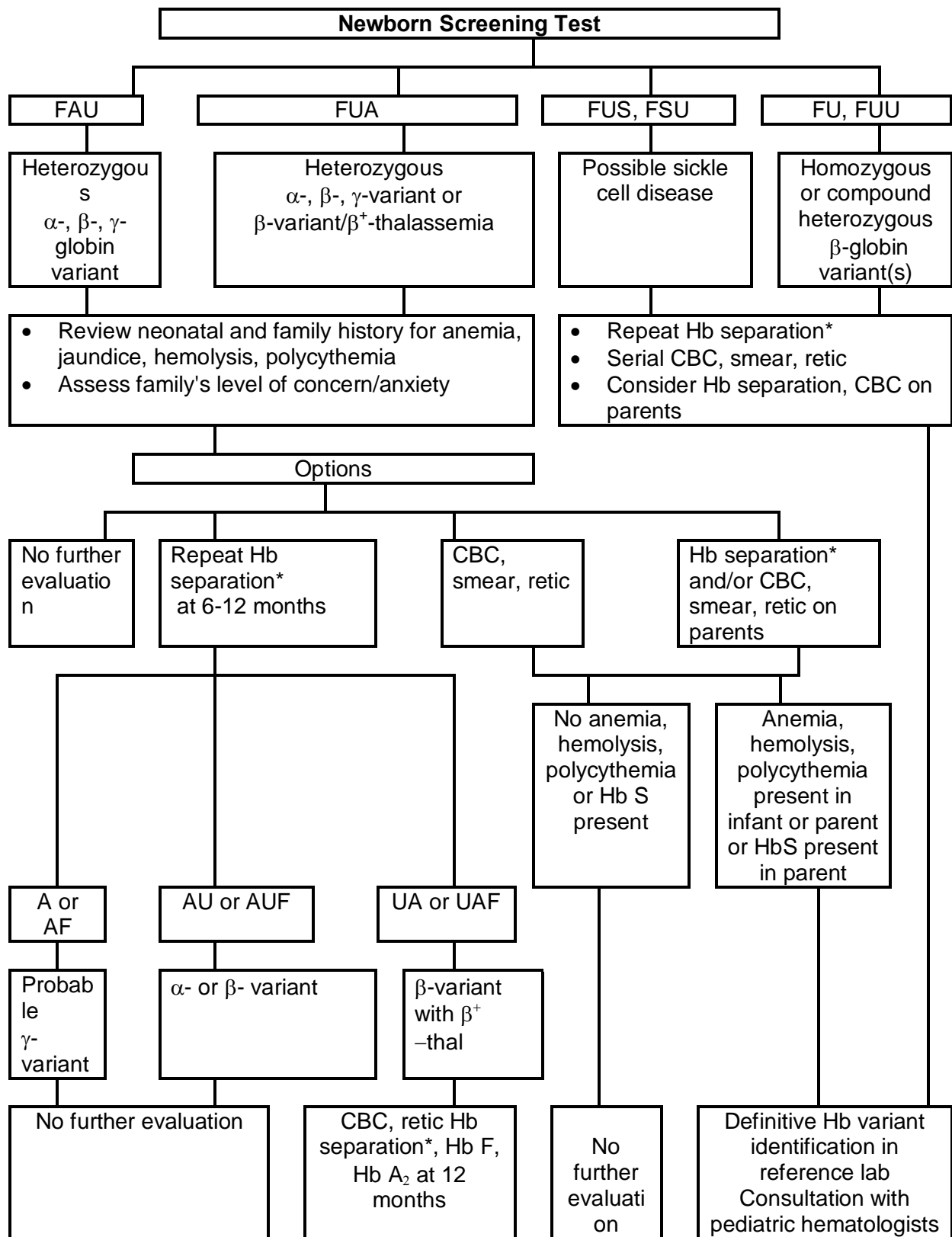
Offer genetic counseling

- * Normal MCV for infants 9-12 months-of-age is ≥ 70 ft. Phone consultation with pediatric hematologist may prove helpful in interpreting results.
- ** Family studies. Initially CBC on parents and other siblings. Subsequent evaluation of couples possibly at risk for hydropic fetus requires DNA studies and possible referral to a perinatal genetics center.

Unidentified Hemoglobin Variants

Each year unidentified (U or "other") hemoglobin variants are detected by neonatal screening in thousands of U.S. infants. Most of these infants are heterozygotes (i.e., screening results FAU). These variants may be caused by mutations in α -, β -, or γ -globin genes. Most have no clinical or hematologic consequence, but a few may show altered oxygen affinity or be chemically unstable. Most unidentified Hb variants have no significant genetic implications, but a few may cause sickle cell disease when co-inherited with hemoglobin S. At present time, there is limited reference laboratory capacity in the United States, such that the majority of unidentified hemoglobin variants identified by screening cannot be definitively identified. Thus, while the overwhelming numbers have no clinical or genetic significance, uncertainty about the identity of variants may lead to frustration and anxiety for families and health care providers.

The following strategy is suggested for the follow-up of unidentified hemoglobin variants identified by newborn screening. The algorithm is intended to provide a common-sense approach that should limit laboratory expense and reserve definitive hemoglobin variant identification in reference labs for situations where definitive identification is needed for specific clinical or genetic concerns in a given family.



* Hb separation by hemoglobin electrophoresis, isoelectric focusing, or HPLC

Genetic Counseling

Hemoglobinopathies and Hemoglobin Traits

1. Genetic counseling should be provided by a medical specialist who has been trained in genetic counseling for hemoglobinopathies. Counseling can be provided by a genetic counselor with expertise in hemoglobinopathies or by a hematologist, pediatrician, nurse, or other medical specialist with expertise in the inheritance of hemoglobinopathies.
2. Patients with clinically significant disease should already be under medical management of a primary care physician, pediatrician and/or hematologist. If possible, all pertinent laboratory tests should have been done previously: newborn screening results (initial and confirmatory), DNA, and/or other hemoglobinopathy testing. (For details of testing potential hemoglobinopathy carriers, see #3 below.) Additional testing may be recommended after evaluation of the family history. These tests may be ordered immediately after counseling or may need to be arranged individually depending upon each person's medical resources.
3. Genetic counseling information should include a review of genetic inheritance, specifically autosomal recessive mode of inheritance, provision of accurate recurrence risk information to parents of an affected member, evaluation of the family history, and discussion of the importance of testing other family members who are at risk for a hemoglobinopathy or to be a carrier. Accurate recurrence risk counseling for parents of a member identified as having sickle cell trait, hemoglobin C trait, or β -thalassemia, etc. requires knowledge of the parents' carrier status. Testing of potential carriers requires a CBC and hemoglobin separation by electrophoresis, isoelectric focusing, and/or HPLC (including accurate quantization of Hb F and Hb A₂ if the MCV is borderline or decreased). Solubility testing (i.e. Sickledex, Sickprep, Sicklequik) is inadequate for hemoglobinopathy screening, and should never be used.
4. Accurate information about the clinical course, treatment, and medical complications of the specific hemoglobin disorder relevant to the family must be provided, with emphasis on the importance of continuing medical follow-up and health maintenance strategies which can help decrease the number and severity of medical complications.
5. If a pregnancy is in progress for a couple at-risk for a member with a hemoglobinopathy, a referral to a prenatal genetics center or to an obstetrician with expertise in prenatal diagnosis should be offered.

SICKLE CELL DISEASE - ROUTINE COMPREHENSIVE EVALUATIONS

(In conjunction with a pediatric hematologist and/or sickle cell program)

Age	Hx(ROS) Psychosocial Exam Education	CB C Reti c	Hb Electr o	RBC Phenoty pe	Chemist ry ¹	U/A	Puls e Ox	CX R	EKG Echo PFT' s	CN S	Gallbladd er Ultrasoun d	Ophth Consu lt
2 mo	X	X										
4 mo	X	X										
6 mo	X	X	2									
9 mo	X	X										
12 mo	X	X	2	X	X		X					
15 mo	X	X										
18 mo	X	X					X					
2-9 yr	3	3	2		4	4	4	5	6	7	8	
≥10 yr	4	4			4	4	4	5	6	7	8	9
New pt	X	X	2	X	X	10	X	10	10	7	10	10

Table provides general guidelines: Schedules for routine clinic visits and studies will need to be modified for individual patients.

- 1 Consider creatinine, BUN, liver function tests. Consider adding ferritin and/or iron and TIBC for any patients at risk for iron deficiency or for those at risk for hemosiderosis secondary to multiple transfusions.
- 2 Patients without documented confirmation of diagnostic testing or for whom diagnosis is unclear (e.g. FS or FSA on neonatal screen without subsequent anemia or hemolysis); review of other hematologic studies and family studies may also help establish accurate diagnosis.
- 3 2-3 times per year
- 4 Yearly
- 5 Consider every other year; yearly if history of recent acute chest syndrome or evidence of chronic cardiac or pulmonary disease

- 6 Consider to document baseline status and evidence of chronic cardiac or pulmonary disease in patients with history of severe or recurrent acute chest syndrome or unexplained cardiopulmonary symptoms.
- 7 May include CNS imaging such as MRI, MRA, and TCD ultrasonography and/or neurocognitive testing. Consider especially for patients with poor school performance or developmental or behavioral concerns.
- 8 prn clinical suspicion of cholelithiasis every 1-2 years as appropriate for age

SICKLE CELL DISEASE - IMMUNIZATIONS AND PROPHYLACTIC MEDICATIONS

(Routine immunizations should be administered per standard guidelines. For issues not covered by the table, consult the latest guidelines of the American Academy of Pediatrics.)

Age	Pneumococcal Conjugate Vaccine (PCV7)*	Pneumococcal Polysaccharide Vaccine	Meningococcal Vaccine	Influenza Vaccine	Penicillin	Folic Acid
2 mo	X				8	
4 mo	X				8	
6 mo	x (1)			7	8	9
12-15 mo	x (2)			7	8	
2 yrs.	3	x (3)	6	7	8	
5 yrs.	4	x (4)	6	7	8	9
>10 yrs.	4	5		7	8	9

* Two different pneumococcal vaccines are now licensed, a new 7-valent pneumococcal conjugate vaccine (PCV7) and the old 23-valent pneumococcal polysaccharide vaccine (PPV23). Four doses of PCV7 are now recommended for all infants and members < 2 yrs. of age. Because of different serotype coverage, members with sickle cell disease should receive both vaccines, but always ≥ 2 months apart.

1. For members 7-11 months of age not previously immunized with PCV7, 2 doses 2 months apart followed by a third dose at 12-16 months.
2. For members 12-23 months of age not previously immunized with PCV7, 2 doses 2 months apart.
3. For members 24-59 months of age previously immunized with PPV23 but not PCV7, 2 doses of PCV7 2 months apart ≥ 2 months after PPV23 Second PPV23 3 years after first PPV23 and ≥ 2 months after second PCV7.

For members 24-59 months of age not previously immunized with PCV7 or PPV23, 2 doses of PCV7 2 months apart, followed by 1 dose of PPV23 ≥ 2 months later and second dose PPV23 3-5 years after the first PPV23.

4. For members ≥ 5 years of age previously immunized with PPV23 but not PCV7, 1 dose of PCV7 ≥ 2 months after last dose of PPV23. If not previously given, second dose of PPV23 ≥ 2 months after PCV7 and 3-5 years (< 10 years of age) or ≥ 5 years (> 10 years of age) after first dose of PPV23.

For members ≥ 5 years of age not previously immunized with PPV23 or PCV7, 1 dose of PCV7 followed by first dose of PPV23 ≥ 2 months later and second dose PPV23 3-5 years (< 10 years of age) or ≥ 5 years (> 10 years of age) after first PPV23.

5. Some centers recommend third dose of PPV23 ≥ 5 years after second dose PPV23.
6. Recommended for asplenic patients by AAP Red Book, but not considered routine standard-of-care at many sickle cell centers.
7. Yearly for members ≥ 6 months of age.
8. Penicillin prophylaxis (125 mg PEN VK po bid < 3 yr; 250 mg po bid > 3 yr) from 2 months to 5 years of age in all infants with Hb SS and S β^0 -thalassemia. Prophylaxis considered on case by case basis for older members (especially those with previous invasive pneumococcal infection or surgical splenectomy) and for those with Hb SC and S β^{+} -thalassemia. Note: tablets have a longer shelf life

than suspension, which must be reconstituted with water, kept refrigerated, and expires in 14 days. Erythromycin may be used as a substitute for members with proven or suspected penicillin allergy.

9. Controversial. Folic acid 400 mcg or 1 mg po q.d. may be considered for members with significant hemolysis (Hb SS, S β^0 -thalassemia).

CRS MANAGED HEALTHCARE SERVICES

SICKLE CELL PATIENT & FAMILY NEEDS ASSESSMENT

Please answer the following questions by circling Y=yes or N=no

Do you have any problems getting good health care for your child? **Y N**

Do you feel comfortable with how well you can treat and control your child's pain at home? **Y N**

Do you know how to take your child's temperature? **Y N**

If your child is less than 5 years old, can you feel the belly for enlargement of the spleen? **Y N**

Are you comfortable with your understanding of sickle cell? **Y N** Do you want more general information? **Y N**

Do you need more information on how sickle cell is inherited? **Y N**

Do you have problems with health insurance? **Y N** with parking? **Y N** with transportation? **Y N**

Do you feel your child's pain problems are treated well when your child is in the hospital? **Y N**

Which emergency room do you use? _____ Are you comfortable with the staff's knowledge of sickle cell disease and the way they control your members pain? **Y N**

Do you feel that the people who work at our clinic understand and are sensitive to your cultural background and needs? **Y N**? Do you feel that you have the opportunity to take part in making decisions about your child's health care? **Y N**

Do you get the kind of help from others that you need? **Y N** If yes, from whom? (circle) Family, Friends, Church, Other: _____

Would you like more contact with another family who has children with sickle cell disease? **Y N**

What is your child's grade in school? _____ Is your child enrolled in special education? **Y N**

Do you feel there is a need for a better understanding of your child's special needs at school? **Y N**
About how many days did your child miss from school last year? _____

If your child is more than 12 years old, are you receiving services to help your child prepare for an independent adult life? **Y N**

Are your other children having any problems because of their brother or sister with sickle cell disease? **Y N**

Are there any other worries in your life? **Y N**

Would you be willing to work toward getting better care and more research on sickle cell disease?
Y N

Are you a member of the Sickle Cell Association? **Y N**

What are the hardest things about sickle cell disease that you have to deal with?

—

—

What else can we do for you?

—

Name of child: _____ Age: _____

Date of Birth: _____

Who completed this form? (Name, relationship to patient) _____

Date _____

ACUTE ILLNESS IN SICKLE CELL DISEASE: Illness Requiring Urgent Medical Care

Definition of illness requiring immediate medical care, including emergencies

Any of the following:

- T > 101°F or 38.5°C
- Pain inadequately relieved by home measures
- Significant respiratory symptoms (e.g., severe cough, shortness of breath, chest pain)
- Abdominal pain, distension, and/or acute enlargement of the spleen
- Any neurologic symptom or sign - even if transient
- Significant increase in pallor, fatigue, and/or lethargy
- Priapism episode lasting > 2-3 hr
- Significant vomiting or diarrhea

Acute illness characterized by any of the signs or symptoms listed above can prove rapidly life-threatening. Thus it is essential that sickle cell patients have unimpeded access to the providers / facility in their community that are best prepared to provide appropriate care. Ideally, every patient should have a predetermined plan to rapidly access an appropriate provider / facility that can provide:

- Expertise in sickle cell disease and/or immediate contact/consultation with a pediatric hematologist or the patient's primary care physician with expertise in sickle cell disease
- Access to patient's baseline data (past problems, exam, lab, radiographs)
- Access to appropriate transfusion support

It is essential that providers of urgent care make contact with the patient's continuity physician or service during the acute illness visit to be certain that appropriate treatment is provided (see clinical care paths, p. 16-25) and that continuity of care is maintained.

TRANSFUSION THERAPY FOR ACUTE COMPLICATIONS

Red blood cell transfusions play an important role in the treatment of some acute illnesses in patients with sickle cell disease. For severe complications, timely transfusions may be life saving. Specific guidelines for the use of transfusions for individual complications are provided in the clinical care paths throughout this manual. In general, appropriate use of red cell transfusions require attention to the following issues:

Indications:

Indications for red cell transfusions include acute exacerbations of the patient's baseline anemia that require increased oxygen carrying capacity, acute life or organ-threatening vaso occlusive episodes, and preparation for surgical or radiographic procedures that involve general anesthesia or the use of ionic contrast.

- Acute exacerbation of baseline anemia
 1. Aplastic crisis
 2. Splenic sequestration
 3. Hepatic sequestration
 4. Hyperhemolysis
- Severe vaso-occlusive events
 1. Acute chest syndrome
 2. Stroke
 3. Severe infection
 4. Acute multiorgan failure syndrome
- Preparation for procedures
 1. General anesthesia and surgery
 2. Radiographs with ionic contrast

Selection of transfusion products

Leukocyte-depleted, packed red blood cells are recommended. Where available, minor-antigen-matched, sickle-negative cells are preferred.

Transfusion method

A simple transfusion is appropriate for most situations characterized by acute exacerbation of anemia. Partial exchange transfusion, generally by erythrocytapheresis, may be needed for severe life-threatening illness or in situations where a relatively high baseline hemoglobin precludes a simple transfusion that would risk hyperviscosity by increasing the hemoglobin level to > 10gm/dl.

Volume considerations

Patients with severe chronic anemia (i.e. aplastic crisis) are at risk for volume overload and congestive heart failure from rapid infusion of RBC. Thus, slow correction of the anemia (e.g., 4-5 cc/kg packed RBC over 4 hr, often with furosemide) or isovolemic partial exchange transfusion may be needed to prevent precipitation of cardiovascular collapse.

Hyperviscosity

Because sickle red cells are poorly deformable, simple red cell transfusions that increase the hemoglobin levels to > 10gm/dl may be associated with hyperviscosity and should be avoided.

OUTPATIENT EVALUATION AND MANAGEMENT OF FEBRILE ILLNESS

(T \geq 101°F or 38.5°C) IN MEMBER WITH SICKLE CELL DISEASE

1. Rapid triage - immediately upon presentation. Place immediately into exam room.
2. Brief history and physical exam with emphasis on:
 - vital signs
 - degree of pallor
 - evidence of systemic or localized infection
 - cardiopulmonary status
 - spleen size (compare with baseline exam)
 - neurologic exam
2. Laboratory:
 - Stat CBC, diff, platelet, reticulocyte count, and blood culture (use butterfly or angiocath and follow immediately with IV antibiotic).
 - Type and crossmatch if extreme pallor, respiratory or neurologic symptoms, or acute splenic enlargement present. Consider requesting, if available, minor-antigen-matched, sickle-negative, and leukocyte-depleted RBC.
 - Urinalysis and urine, CSF, other cultures if clinically indicated.
4. Prompt administration of IV ceftriaxone (50-75 mg/kg, 2.0 grams maximum single dose) through butterfly or IV catheter used for phlebotomy. (For patients with known or suspected cephalosporin allergy, substitute clindamycin 10-15 mg/kg, 600 mg maximum single dose.)
 - Strongly consider adding vancomycin (10-15 mg/kg IV) for severe illness or if CNS infection is suspected.
 - Parenteral antibiotics should be given before other procedures, such as CXR, etc.
 - *The presence of a focus of infection (e.g. otitis) does not alter the urgency of giving parenteral antibiotics.*
5. Acetaminophen 15 mg/kg po (if not given in the last 4 hr) and/or ibuprofen 10 mg/kg po. Avoid ibuprofen if contraindication present (i.e. gastritis, ulcer disease, coagulopathy, or renal impairment).
6. Review summary of patient's last comprehensive evaluation or seek baseline information by phone.
7. Contact pediatric hematologist or patient's primary physician with expertise in sickle cell disease.
8. CXR and pulse ox (or blood gas), particularly if:
 - toxic appearance
 - any respiratory symptoms
 - chest and/or abdominal painMay use O₂ by nasal cannula or face mask if signs of respiratory illness present. The etiology of a supplemental O₂ requirement should be investigated.
9. Observation:

a) Admission:

1. Most infants < 1 yr with HbSS or S β^0 -thalassemia
2. Most with previous episodes of bacteremia or sepsis
3. Most with T > 40°C, WBC > 30,000/mm³ or < 5,000/mm³, and/or platelet count < 100,000/mm³
4. Signs of systemic toxicity
5. Patients who receive clindamycin or vancomycin
6. Evidence of other acute complications including severe pain, aplastic crisis, splenic sequestration, acute chest syndrome, stroke, or priapism (see other Clinical Care Paths).
7. Concerns about compliance / follow-up

b) Outpatients:

Observe with repeat vital signs and assessment ≥ 2 hr post ceftriaxone. If non-toxic and clinically stable with reliable family and hematologist/PCP approval, discharge with a specific plan for outpatient follow-up. Minimum follow-up includes phone contact the next day. Repeat exam and 2nd dose of ceftriaxone (with or without repeat CBC and reticulocyte count) 24 hr later may be advisable in some cases.

INPATIENT MANAGEMENT OF FEVER IN MEMBER WITH SICKLE CELL DISEASE

CONSULTS:

Hematology

MONITORING:

1. Vital signs q 2 hr until stable, then q 4 hr (suspect septic shock)
2. Consider CR monitor and ICU for any signs of cardiovascular instability.
3. Record I & O, daily weight.
4. Pulse ox for severe illness or if respiratory signs or symptoms present.

DIAGNOSTICS (if not previously obtained):

1. CBC, diff, platelet, and reticulocyte count initially and daily until improving (compare with patient's baseline data).
2. CXR if tachypnea, cough, chest or abdominal pain, or any respiratory symptoms are present or subsequently develop.
3. Blood culture if febrile. Consider urinalysis, urine and other cultures (e.g. CSF).
4. Consider renal and liver function tests (BUN, creatinine, fractionated bili, ALT) and DIC screen for very severe pain or any evidence of encephalopathy (R/O acute multi-organ failure syndrome).
5. Consider abdominal ultrasound, liver function tests, amylase and lipase for RUQ, epigastric or severe abdominal pain (R/O cholelithiasis, cholecystitis, pancreatitis).
6. Type and crossmatch if Hb is 1-2 gm/dl or more below baseline or if evidence of acute chest syndrome present (see acute chest syndrome care path). Consider requesting, if available, minor-antigen-matched, sickle-negative, and leukocyte-depleted RBC.
7. Consider orthopedic consult with aspiration for culture of bone or joint if osteomyelitis or septic arthritis suspected.

FLUIDS, GENERAL CARE:

IV + PO 1-12 x maintenance. Increased fluids may be needed if patient is dehydrated or if insensible losses are increased (e.g. persistent fever). Avoid excessive fluids, which may precipitate or exacerbate acute chest syndrome.

MEDICATION/TREATMENT:

1. Cefotaxime or cefuroxime 50 mg/kg IV q 8 h or Certraxone 50 mg/kg/dose q 24 hrs.. Substitute clindamycin 10 mg/kg IV q 6 hr for patients with known or suspected cephalosporin allergy. Strongly consider adding vancomycin 10-15 mg/kg IV q 8 hr for severe illness and/or proven or suspected CNS infection. Prophylactic penicillin should be discontinued while patient is receiving broad-spectrum antibiotics.
2. Acetaminophen 15 mg/kg po q 4 hr. May add ibuprofen 10 mg/kg po q 6-8 h if no contraindication (i.e. gastritis, ulcer, coagulopathy, or renal impairment). Limit more frequent dosing to 72 hr maximum duration.
3. See other Clinical Care Paths for pain, acute chest syndrome, acute anemic crisis, stroke, priapism, if present.
4. O₂ by nasal cannula or face mask if needed to keep pulse ox $\geq 92\%$ or \geq patient's baseline value (if $> 92\%$). The etiology of a new or increasing supplemental O₂ requirement should be investigated. Avoid excessive or unnecessary O₂, which may suppress the reticulocyte count and exacerbate anemia.
5. Consider transfusion with RBC if Hb is 1-2 gm/dl or more below baseline and patient shows any signs of cardiovascular compromise.

DISCHARGE CRITERIA:

1. Afebrile ≥ 24 hr with negative cultures $\geq 24-48$ hr.
2. Taking adequate oral fluids and able to take po medications (e.g. prophylactic penicillin) if applicable.
3. Resolution of any pulmonary symptoms or documentation of adequate oxygenation on room air.
4. No evidence of anemic crisis (aplastic or sequestration): stable hemoglobin/hematocrit.
5. Follow-up arranged.

OUTPATIENT EVALUATION AND MANAGEMENT OF PAIN IN MEMBER WITH SICKLE CELL DISEASE

1. History:

- Nature, location, duration, and severity of pain
- Character of pain similar to previous sickle pain?
- Analgesics already used for this episode
- Associated symptoms - especially fever or evidence of dehydration
- Consider etiologies other than sickling (e.g., cholecystitis, appendicitis, trauma)
- Previous experience with analgesics (efficacy and side effects). What does patient/family feel best alleviates pain?

2. Physical Exam: Complete with emphasis on:

- vital signs
- hydration status
- degree of pallor
- evidence of infection
- cardiopulmonary status
- spleen size (compare with baseline exam)
- penis (priapism)
- neurologic

3. Lab:

- CBC, diff, platelet, and reticulocyte count (compare with patient's baseline values)
- Blood cultures if febrile (see fever care path)
- Type and crossmatch if extreme pallor, respiratory or neurologic symptoms, or acute splenic enlargement present. Consider requesting, if available, minor-antigen-matched, sickle-negative, and leukocyte-depleted RBC.
- CXR and pulse ox (or blood gas) if:
 - Fever
 - chest pain
 - tachypnea
 - respiratory symptoms
- Consider abdominal ultrasound and liver function tests for RUQ, epigastric pain (R/O choletithiasis /cholecystitis).

4. Contact pediatric hematologist or patient's primary physician with expertise in sickle cell disease.

5. Treatment (discuss with patient, family, and hematologist or primary physician on-call)

a) Mild to moderate pain:

- “ Acetaminophen with codeine 1 mg/kg po (and then q 4 hr) and oral fluids
- “ Consider starting ibuprofen 10 mg/kg po q 6-8 h or other anti-inflammatory agent if no contraindication (i.e. gastritis, ulcer, coagulopathy, or renal impairment). Limit more frequent dosing to 72 hr maximum duration.
- “ If adequate relief and no other acute complications present, discharge on oral analgesics (acetaminophen with codeine and/or ibuprofen).

- “ If inadequate relief within 30 min, follow b, below
- “ Ibuprofen or other NSAID as first line treatment for mild to moderate pain.

b) Moderate to severe pain:

- Morphine 0.1-0.15mg/kg IV. Reassess pain q 15-30 min. Patients with severe pain may require repeated doses of morphine 0.02-0.05 mg/kg IV q 15-30 min to achieve pain relief. Alternative analgesics, such as hydromorphone (Dilaudid) 0.015-0.02 mg/kg IV, may be appropriate in individual cases. Ketorolac (Toradol) 0.5 mg/kg (30 mg maximum dose) IV may be used in addition to opioid analgesia if no contraindication (i.e., gastritis, ulcer, coagulopathy, or renal impairment). Do not use ibuprofen with ketorolac. Repeated doses of meperidine (Demerol) should be avoided because of the risk of seizures.
- IV fluids: 10 cc/kg bolus over 1 hr then maintenance rate. Excessive fluids should be avoided unless patient is judged dehydrated.
- Monitor pulse ox. Use O₂ by nasal cannula or face mask if needed to keep O₂ saturation ≥ 92% or ≥ patient's baseline value (if > 92%). The etiology of a supplemental O₂ requirement should be investigated.
- If adequate pain relief with one or two doses of morphine, consider giving acetaminophen with codeine (1 mg/kg) as outpatient therapy.
- Consider hospitalization for around-the-clock parenteral analgesics if more than one or two doses of morphine required.

INPATIENT MANAGEMENT OF VASO-OCCLUSIVE PAIN IN MEMBER WITH SICKLE CELL DISEASE

CONSULTS:

Hematology

MONITORING:

1. Vital signs q 4 hr
2. Record I+O, daily weight
3. Strongly consider continuous pulse ox if any respiratory symptoms present or if on parenteral narcotics
4. Consider CR monitor

DIAGNOSTICS (If not previously obtained):

1. CBC, diff, platelet count, and reticulocyte count initially and daily until improving. (Compare with patient's baseline data.)
2. CXR if cough, chest pain, hypoxemia or any respiratory symptoms present or develop after admission. Patients with severe vaso-occlusive pain are at increased risk for acute chest syndrome (see p. 20).
3. If febrile, blood culture and other cultures (e.g. urine, CSF) and urinalysis as indicated.
4. Consider renal (BUN, Creat) and liver (fractionated bili, ALT) function tests for very severe pain or any evidence of encephalopathy (R/O acute multi-organ failure syndrome).
5. Consider abdominal ultrasound, liver function tests, and/or amylase and lipase for RUQ, epigastric or severe abdominal pain (R/O cholelithiasis, cholecystitis, pancreatitis)
6. Type and crossmatch if Hb is 1.5-2.0 gm/dl or more below baseline and/or if evidence of acute chest syndrome (see acute chest syndrome care path) or cardiovascular compromise present. Consider requesting, if available, minor-antigen-matched, sickle-negative, and leukocyte-depleted RBC.

FLUIDS, GENERAL CARE:

1. IV + P.O. 1-12 x maintenance. Increased fluids may be needed if patient is dehydrated and/or insensible losses are increased (e.g., persistent fever). Avoid excessive fluids, which may precipitate or exacerbate acute chest syndrome.
2. Incentive spirometry - 10 breaths q 2 hr when awake
3. Encourage ambulation and activity

MEDICATION/TREATMENT:

1. Morphine sulfate 0.05 - 0.15 mg/kg/dose IV q 2 hr or 0.05 - 0.1 mg/kg/hr continuous infusion or via PCA. (For PCA give 1/3-1/2 of total maximum dose by continuous infusion, with 1/2-2/3 via PCA boluses.) Total morphine dose, continuous infusion plus boluses, above 0.1 mg/kg/hr may occasionally be required but should be used with caution. In most cases, prn analgesic orders are not appropriate. Alternative analgesics including hydromorphone (Dilaudid) 0.015-0.02 mg/kg IV q 3-4 hr may be appropriate in selected cases. Consider use of ketorolac (Toradol) 0.5 mg/kg (30 mg maximum dose) IV q 6-8 hr in addition to opioid analgesia if no contraindication (i.e. gastritis, ulcer, coagulopathy, or renal impairment). Do not use ibuprofen with ketorolac. Repeated doses of meperidine (Demerol) should be avoided because of the risk of seizures. Base choice of analgesics in part or prior experience of patient with efficacy and side effects. Consider the addition of naloxone (Narcan) drip at 0.25 mcg/kg/hour with continuous drip opioids to prevent itching and constipation.

2. Ibuprofen 10 mg/kg po q 6-8 hr or other anti-inflammatory agent if no contraindication (i.e. ketoralac, gastritis, ulcer, coagulopathy, or renal impairment). Limit more frequent dosing to 72 hr maximum duration.
3. Cefotaxime or cefuroxime 50 mg/kg IV q 8 h or Ceftriaxone 50 mg/kg/dose q 24 hours if febrile. Substitute clindamycin 10 mg/kg IV q 6 hr for known or suspected cephalosporin allergy. Strongly consider adding vancomycin 10-15 mg/kg IV q 8 h for severe febrile illness or for proven or suspected CNS infection.
4. If applicable, continue prophylactic penicillin. Prophylactic penicillin should be discontinued while patient is receiving broad-spectrum antibiotics.
5. Consider pain team consultation.
6. O₂ by nasal cannula or face mask as needed to keep pulse ox \geq 92% or \geq patient's baseline value (if > 92%). The etiology of a new or increasing supplemental O₂ requirement should be investigated. Avoid excessive or unnecessary O₂, which may suppress the reticulocyte count and exacerbate anemia.
7. Offer heating pads or other comfort measures previously used by patient.
8. Consider colace or laxative for narcotic-induced constipation.
9. See other Clinical Care Paths for acute chest syndrome, acute splenic sequestration, aplastic crisis, stroke, priapism, if present.
10. Reassess pain control on a regular basis (at least twice daily) by discussing efficacy and side effects with patient/family. Analgesics may be weaned as tolerated by decreasing dose, not by prolonging interval between doses. Discuss analgesic changes with patient/family.

DISCHARGE CRITERIA:

1. Adequate pain relief on oral analgesics.
2. Taking adequate oral fluids and be able to take po medications (e.g. prophylactic penicillin) if applicable.
3. Afebrile \geq 24 hr. with negative cultures for \geq 24-48 hr. if applicable.
4. Resolution of any pulmonary symptoms or documentation of adequate oxygenation on room air.
5. Stable hemoglobin/hematocrit
6. Follow-up arranged.

CRS MANAGED HEALTHCARE SERVICES

ACUTE CHEST SYNDROME IN MEMBER WITH SICKLE CELL DISEASE

DEFINITION:

An acute illness associated with lower respiratory symptoms, hypoxemia, or new infiltrate on CXR.

CONSULTS:

Hematology

MONITORING:

1. Hospitalize
2. Vital Signs q 2-4 hr
3. Continuous pulse ox
4. Record I+O, daily weight

DIAGNOSTICS:

1. CBC, diff, platelet count, and reticulocyte count initially and daily until improving. (Compare with patient's baseline values.)
2. CXR initially, repeat for clinical deterioration
3. Consider:
 - a) Type and crossmatch for severe illness or if Hb > 1 gm/dl below baseline. Consider requesting, if available, minor-antigen-matched, sickle-negative, and leukocyte-depleted RBC.
 - b) Blood cultures if febrile or history of recent fever
 - c) Blood gas for severe illness
 - d) Renal (BUN, creat) and liver (fractionated bili, ALT) function tests for severe illness or if diffuse encephalopathy present (R/O acute multiorgan failure syndrome)

FLUIDS, NUTRITION, GENERAL CARE:

1. Maintain "euvolemia". IV + P.O. 1-13 x maintenance. More fluid is appropriate only if patient is dehydrated or if insensible losses are increased (e.g., persistent fever).
2. Incentive spirometry - 10 breaths q 2 h when awake
3. Encourage ambulation, activity

MEDICATIONS/TREATMENTS:

1. Oxygen to pulse ox $\geq 92\%$ or \geq baseline value (if $> 92\%$).
2. Acetaminophen 15 mg/kg po q 4 hr. or prn $T > 38.0^{\circ}\text{C}$
3. Ibuprofen 10 mg/kg po q 6-8 hr if no contraindication (i.e., ketorolac, gastritis, ulcer, coagulopathy, renal impairment). Limit more frequent dosing to 72 hr maximum duration.
4. Morphine 0.05 - 0.15 mg/kg IV q 2 hr or 0.05 - 0.1 mg/kg/h continuous infusion or PCA for severe pain. (For PCA give 1/3-1/2 of total maximum dose by continuous infusion and 1/2-2/3 via PCA boluses.) Total morphine dose, continuous infusion plus boluses, above 0.1 mg/kg/hr may occasionally be required but should be used with caution. Alternative analgesics including hydromorphone (Dilaudid) 0.015-0.02 mg/kg IV q 3-4 hr may be appropriate in selected cases. Consider use of ketorolac 0.5 mg/kg (30 mg maximum dose) IV q 6-8 h (72 h maximum duration) to reduce or avoid opioids. Do not use ibuprofen with ketorolac.

5. Cefotaxime or cefuroxime 50 mg/kg q 8 h IV or Ceftriaxone 50 mg/kg/dose q 24 hours. Substitute clindamycin 10 mg/kg IV q 6 h for patient with known suspected cephalosporin allergy. Prophylactic penicillin should be discontinued while patient is receiving broad-spectrum antibiotics.
6. Azithromycin 10 mg/kg po first dose, then 5 mg/kg qd, erythromycin 10 mg/kg q 6 h po, or other macrolide antibiotic
7. Strongly consider adding vancomycin 10-15 mg/kg IV q 8 hr for severe illness, or nafcillin or vancomycin if large infiltrate with pleural effusion present.
8. Consider one dose of furosemide 0.5-1.0 mg/kg IV if signs of fluid overload present.
9. Consider trial of bronchodilators, especially if patient has history of reactive airway disease or wheezing on exam.
10. Consider red cell transfusion:
 - a. Simple transfusion for moderately severe illness, especially if Hb > 1 gm/dl below baseline (do not transfuse acutely to Hb > 10 gm/dl, Hct > 30%).
 - b) Partial exchange transfusion to Hb 10 gm/dl and Hb S or Hb S+C (patient's RBC) ≥ 30% for severe or rapidly progressive disease (may require transfer to ICU and transfusion medicine consult for erythrocytapheresis). Remove femoral or central venous catheters as soon as possible after exchange transfusion to reduce risk of thrombosis.
11. See other Clinical Care Paths for acute splenic sequestration, aplastic crisis, stroke, priapism, if present.

DISCHARGE CRITERIA:

1. Off supplemental O₂.
2. Afebrile ≥ 24 hr. and negative cultures for ≥ 24-48 hr if applicable.
3. Stable hemoglobin/hematocrit.
4. Taking adequate oral fluids and able to take po medications if applicable.
5. Adequate pain relief, if needed, with oral analgesics.
5. Follow-up plans coordinated with hematology service. On a case by case basis, consider follow-up pulmonary function testing and the possibility of chronic transfusions (p. 27) or hydroxyurea (p. 28).

ACUTE SPLENIC SEQUESTRATION IN MEMBER WITH SICKLE CELL DISEASE

DEFINITION:

An acute illness associated with Hb 2 gm/dl or more below patient's baseline value with acutely enlarged spleen. Mild to moderate thrombocytopenia is often present. Reticulocytosis equal to or greater than baseline is usually present. If reticulocyte count is decreased, consider coexistent aplastic crisis (see p.22).

CONSULTS:

Hematology

MONITORING:

1. Hospitalize
2. Consider ICU admission for signs of cardiovascular compromise.
3. Vital signs q 2 hr until stable, then q 4 hr.
4. CR monitor
5. Continuous pulse ox
6. Record I+O, daily weight
7. Serial exams (initially q 2-4 h) to reassess cardiovascular status and spleen size

DIAGNOSTICS:

1. CBC, diff, platelet count, and reticulocyte count initially, then q 4-12 hr depending on severity of anemia, rate of fall in Hb level, changes in spleen size.
2. Type and crossmatch RBC stat. Time permitting, consider if available minor-antigen-matched, sickle-negative, and leukocyte-depleted RBC.
3. Blood culture, urinalysis, and urine culture if febrile. Consider CSF and other cultures.
4. Consider CXR if febrile or if any signs or symptoms of respiratory illness present.

FLUIDS, GENERAL CARE:

1. IV + PO @ 1 X maintenance. More fluids may be needed if insensible losses are increased (e.g. persistent fever) or to support intravascular volume before transfusion.
2. Incentive spirometry - 10 breaths q 2 hr when awake if on parenteral narcotics.

MEDICATION/TREATMENT:

1. RBC transfusions 10 cc/kg for Hb < 4-5 gm/dl and/or signs of cardiovascular compromise; will often give 5ml/kg or PRBCs in 2 increments to prevent volume overload if cells released from the spleen. *In severe cases, urgent initiation of transfusion prior to inpatient admission may be life-saving.*
2. Cefotaxime or cefuroxime 50 mg/kg IV q 8 hr or Ceftriaxone 50mg/kg if febrile. Substitute clindamycin 10 mg/kg IV q 6 h for patients with known or suspected cephalosporin allergy. Strongly consider adding vancomycin 10-15 mg/kg IV q 8 hr for severe febrile illness or for proven or suspected CNS infection.
3. If applicable, continue prophylactic penicillin. Penicillin prophylaxis should be discontinued while patient is receiving broad-spectrum antibiotics.
4. O₂ by nasal cannula or face mask if needed to keep pulse ox \geq 92% or \geq patient's baseline value (if > 92%). The etiology of a new or increasing supplemental O₂ requirement should be investigated. O₂ @ 2 liters by nasal cannula or 35% by face mask can be given empirically for the severely anemic member who is to receive RBC transfusions.
5. Acetaminophen 15 mg/kg po q 4 hr and/or ibuprofen 10 mg/kg po q 8 hr for any fever and/or mild pain. (Hyperthermia may exacerbate cardiovascular compromise with severe anemia.)

6. Morphine sulfate 0.05-0.15 mg/kg IV q 2 hr or 0.05-0.1 mg/kg/hr continuous infusion or via PCA for severe pain. (For PCA give 1/3-1/2 of total maximum dose by continuous infusion and 1/2-2/3 via PCA boluses.) Total morphine dose, continuous infusion plus boluses, above 0.1 mg/kg/hr may occasionally be required but should be used with caution. Alternative analgesics including hydromorphone (Dilaudid) 0.015-0.02 mg/kg IV q 3-4 hr may be appropriate in selected cases.
7. See other Clinical Care Paths for vaso-occlusive pain, acute chest syndrome, aplastic crisis, stroke, priapism, if present.

DISCHARGE CRITERIA:

1. Stable hemoglobin/hematocrit.
2. Taking oral fluids well and able to take po medications (e.g. prophylactic penicillin) if applicable.
3. Afebrile ≥ 24 hr. and negative cultures for $\geq 24-48$ hr. if applicable.
4. Adequate pain relief, if needed, with oral analgesics.
5. Follow-up arranged.
6. Consider surgical splenectomy and/or chronic transfusions for severe or recurrent events.

APLASTIC CRISIS IN MEMBER WITH SICKLE CELL DISEASE

DEFINITION:

An acute illness associated with Hb below patient's baseline value with a substantially decreased reticulocyte count (often < 1%). Most cases are caused by acute infection with human parvovirus. If acute enlargement of spleen is present, consider coexistent splenic sequestration (see p. 21). Parvovirus also has been associated with other acute complications of sickle cell disease which may occur during aplastic crisis, including pain, bone marrow necrosis, acute chest syndrome, and stroke.

CONSULTS:

Hematology

MONITORING:

1. Hospitalize for evidence of cardiovascular compromise, for inability to provide appropriate transfusion support as outpatient, and/or for concerns about reliability of follow-up.
2. Vital signs q 2 hr until stable, then q 4 hr. if hospitalized.
3. Consider CR monitor and continuous pulse ox
4. Record I+O, daily weight

DIAGNOSTICS:

1. CBC, diff, platelet count, and reticulocyte count initially, then q 12-24 hr.
2. Type and crossmatch. Consider requesting, if available, minor-antigen-matched, sickle-negative, and leukocyte-depleted RBC.
3. Blood culture, urinalysis, and urine culture if febrile. Consider CSF and other cultures.
4. Consider CXR if febrile or if any signs or symptoms of respiratory illness present.
5. Consider diagnostic tests for parvovirus.

FLUIDS, GENERAL CARE:

1. IV + PO @ 1 X maintenance. More fluids may be needed if insensible losses are increased (e.g. persistent fever). Avoid excessive fluids which may precipitate congestive heart failure.
2. Contact isolation for presumed parvovirus infection (no pregnant care providers).
3. Incentive spirometer 10 breaths q 2 hours while awake.

MEDICATION/TREATMENT:

1. RBC transfusions for symptomatic anemia and/or Hb < 5 gm/dl with no evidence of erythroid recovery; usually 5-6 cc/kg over 4 hrs with close observation for fluid overload. Transfusion may need to be repeated.
2. Cefotaxime or cefuroxime 50 mg/kg IV q 8 hr if febrile. Substitute clindamycin 10 mg/kg IV q 6 hr for patients with known or suspected cephalosporin allergy. Strongly consider adding vancomycin 10-15 mg/kg IV q 8 hr for severe febrile illness and/or for proven or suspected CNS infection.
3. If applicable, continue prophylactic penicillin. Prophylactic penicillin should be discontinued while patient is receiving broad-spectrum antibiotics.
4. O₂ by nasal cannula or face mask if needed to keep pulse ox $\geq 92\%$ or \geq patient's baseline value (if > 92%). The etiology of a new or increasing supplemental O₂ requirement should be investigated. O₂, 2 liters by nasal cannula or 35% by face mask, can be given empirically for the severely anemic member who is to receive RBC transfusions.
5. Acetaminophen 15 mg/kg po q 4 hr and/or ibuprofen 10 mg/kg po q 8 hr for any fever and/or mild pain. (Hyperthermia may exacerbate cardiovascular compromise with severe anemia.)
6. See other Clinical Care Paths for vaso-occlusive pain, acute chest syndrome, acute splenic sequestration, stroke, priapism, if present.

7. CBC and reticulocyte count now and again in 10-14 days on siblings or close contacts with sickle cell disease or other chronic hemolytic anemias to exclude simultaneous or sequential parvovirus infection.

DISCHARGE CRITERIA:

1. Taking adequate oral fluids and able to take po medications (e.g. prophylactic penicillin) if applicable.
2. Adequate pain relief, if needed, with oral analgesics.
3. Afebrile ≥ 24 hours with negative cultures for $\geq 24-48$ hr. if applicable.
4. Adequate hemoglobin/hematocrit with reliable family and outpatient follow-up in place, including arrangements for follow-up clinical and laboratory monitoring and for additional transfusions if needed.

ACUTE STROKE OR NEUROLOGIC EVENT IN MEMBER WITH SICKLE CELL DISEASE

CONSULTS:

Hematology
Neurology
Physical Medicine and Rehabilitation

MONITORING:

1. Rapid triage - urgent hematology consultation
2. Hospitalize. Consider ICU admission and/or CR monitor first 24 hr and until stable.
3. Vital signs, neuro checks q 2 hr.
4. Record I & O, daily weight.

DIAGNOSTICS:

1. Type and crossmatch for partial exchange transfusion (erythrocytapheresis). Consider requesting, if available, minor-antigen-matched, sickle-negative, and leukocyte-depleted RBC.
2. CBC, diff, platelet count, and reticulocyte count initially and as clinically indicated (compare with patient's baseline data).
3. RBC minor-antigen phenotype if not previously documented.
4. Consider screening coagulation profile.
5. Blood and urine cultures if febrile.
6. Electrolytes initially and daily until stable.
7. MRI and MRA. If not immediately available, CT without contrast to exclude intracranial hemorrhage. Initiation of transfusion therapy should not be delayed by arrangements for imaging studies.
8. Consider CSF culture if febrile and no contraindication present.

FLUIDS, GENERAL:

1. IV + PO 1 x maintenance

MEDICATION/TREATMENT:

1. Partial exchange transfusion or erythrocytapheresis to Hb 10 gm/dl and Hb S (patient's RBC) $\leq 30\%$ (may require transfusion medicine consult for erythrocytapheresis). Remove femoral or central venous catheter as soon as possible after exchange transfusion to reduce risk of thrombosis.
2. Simple transfusion with RBC to Hb approximately 10 gm/dl may be considered as an alternative to partial exchange transfusion for stable patients with Hb < 6-7 gm/dl (do not transfuse acutely to Hb > 10 gm/dl, Hct > 30%).
3. Rx seizures if present.
4. Rx increased intracranial pressure if present.
5. O₂ by nasal cannula or face mask if needed to keep pulse ox $\geq 92\%$ or \geq patient's baseline (if > 92%). The etiology of a new or increasing supplemental O₂ requirement should be investigated.
6. Consider hemoglobin electrophoresis after partial exchange transfusion or at discharge.
7. Cefotaxime or cefuroxime 50 mg/kg IV q 8 h or Ceftriaxone 50mg/kg/dose q 24 hours if febrile. Substitute clindamycin 10 mg/kg IV q 6 hr for known or suspected cephalosporin allergy. Strongly consider adding vancomycin 10-15 mg/kg IV q 8 hr for severe febrile illness or for proven or suspected CNS infection.
8. If applicable, continue prophylactic penicillin. Prophylactic penicillin should be discontinued while patient is receiving broad-spectrum antibiotics.

9. See other Clinical Care Paths for pain, acute chest syndrome, acute splenic sequestration, aplastic crisis, priapism, if present.

DISCHARGE CRITERIA:

1. Clinically and neurologically stable > 24 hr. after transfusions.
2. Afebrile > 24 hr. with negative cultures for \geq 24-48 hr. if applicable.
3. Taking adequate oral fluids and able to take oral medication if applicable.
4. Hematology rehabilitation, and physical therapy follow-up organized.
5. Initiate chronic transfusion program (see p. 27).

OUTPATIENT MANAGEMENT OF PROLONGED PRIAPISM IN MEMBER WITH SICKLE CELL DISEASE

Priapism is a prolonged painful erection of the penis that commonly occurs in children and adolescents with sickle cell disease, often starting during the early morning hours. It occurs in two forms: (a) stuttering episodes that last less than 2-4 hours but are often recurrent and may precede a severe episode, and (b) severe events that last more than 2-4 hours and may eventually result in impotence. Simple maneuvers such as increasing oral fluids, taking analgesics, urination, moderate exercise, and/or taking a bath or shower may help end an episode of priapism, and no further specific intervention may be required. Patients who have frequent episodes (≥ 2 within one month or ≥ 4 within one year) should contact their sickle cell program for elective evaluation. For such patients, priapism prophylaxis with pseudoephedrine 30 mg/po hs (< 10 years) or 60 mg/po hs (> 10 years) should be considered. **Any episode that lasts longer than 2-4 hours should be considered an emergency that requires prompt medical intervention as described below.**

1. Rapid triage - immediately upon presentation. Place immediately into exam room.
2. History with emphasis on:
 - length of current episode
 - associated symptoms - especially fever, dysuria, evidence of dehydration, or pain in other locations
 - history of prior episodes of priapism, previous treatments and effectiveness
3. Physical Examination with emphasis on:
 - vital signs
 - hydration status
 - degree of pallor and cardiopulmonary status
 - genitourinary (severity of pain, any evidence of detumescence)
4. Laboratory:
 - consider CBC, diff, platelet, reticulocyte count (compare with patient's baseline values)
 - blood cultures if febrile (see fever care path, p. 16)
 - urinalysis and urine culture for history of dysuria or fever
 - type and cross match if extreme pallor, respiratory or neurologic symptoms, or acute splenic enlargement present. Consider requesting, if available, minor antigen matched, sickle negative, and leukocyte-depleted RBCs.
5. Immediately contact urologist to perform aspiration and irrigation, described below.
6. Review summary of patient's last comprehensive evaluation or seek baseline information by phone.
7. Contact pediatric hematologist or patient's primary care physician with expertise in sickle cell disease.
8. Treatment (discuss with patient, family, and hematologist or primary physician on-call)
 - IV fluids: 10 cc/kg bolus over one hour then at maintenance rate

- analgesia: for moderate to severe pain, morphine 0.1-0.15 mg/kg IV. Reassess pain q 15-30 minutes. Patients with severe pain may require repeated doses of morphine 0.02-0.05 mg/kg IV q 15-30 minutes to achieve pain relief
 - monitor pulse ox for patients receiving opioid analgesia
 - use O₂ by nasal cannula or face mask as needed to keep O₂ saturation ≥ 92 or \geq patient's baseline value (if $> 92\%$).
9. Aspiration and irrigation: The following procedure should be performed by a staff urologist or experienced urology resident as soon as possible for episodes that have lasted more than 4 hours from onset of erection. Conscious sedation may be appropriate for selected patients if administered by experienced staff, but usually is not required.
- the lateral side of the penis is prepped with betadine and approximately 0.5 ml of 1% lidocaine is infiltrated subcutaneously into the lateral surface of the penis and then more deeply into the tunica albuginea.
 - a 23 gauge needle is inserted into the corpora cavernosa and as much blood as possible is aspirated into a dry 10 ml syringe through a three-way stopcock.
 - another 10 ml syringe containing 1:1,000,000 solution of epinephrine (i.e. 1ml of 1:1,000 epinephrine diluted in 1 liter of normal saline) is attached to the three-way stopcock. The corpora cavernosa are irrigated with 10 ml of the 1:1,000,000 epinephrine solution, with additional blood aspirated via dry syringes until detumescence has occurred
 - the needle is withdrawn and five minutes of firm pressure (timed by the clock) is applied by the physician doing the procedure to prevent hematoma.
 - if the patient retains detumescence for ≥ 1 hour they may be discharged home with hematologist/urologist/PCP approval and a specific plan for outpatient follow-up.
 - any recurrent episode lasting > 2 hours should be treated with repeat aspiration and irrigation.
 - If the episode fails to respond to aspiration and irrigation, the patient should be hospitalized for inpatient management (p. 25).

INPATIENT MANAGEMENT OF PROLONGED PRIAPISM IN MEMBER WITH SICKLE CELL DISEASE

DEFINITION:

Prolonged priapism is a painful erection of the penis that lasts more than 2-4 hours and may result eventually in impotence. Most episodes are successfully treated with outpatient aspiration and irrigation with epinephrine (see p.24). This inpatient care path is for patients who fail to respond to outpatient management.

CONSULTS:

1. Hematology
2. Urology

MONITORING:

1. Vital signs q 2-4 h.
2. Record I+O, daily weight.
3. Strongly consider continuous pulse ox if receiving parenteral narcotics.

DIAGNOSTICS (if not previously obtained):

1. CBC, diff, platelet count, and reticulocyte count initially and daily until improving. (Compare with patient's baseline data.)
2. Consider type and crossmatch. Consider requesting, if available, minor-antigen-matched, sickle-negative, and leukocyte-depleted RBC.
3. Urinalysis and urine culture.
4. Blood culture if febrile. Consider other cultures (e.g. CSF).

FLUIDS, GENERAL CARE:

1. IV fluids - 10 cc/kg over 1 hr, then IV + PO = 1½ x maintenance
2. Encourage ambulation
3. Incentive spirometry - 10 breaths q 2 hr when awake if on parenteral narcotics

MEDICATION/TREATMENT:

1. Never use ice or cold packs.
2. Morphine sulfate 0.05-0.15 mg/kg/dose IV q 2 hr or 0.05-0.1 mg/kg/hr continuous infusion or via PCA. (For PCA give 1/3-1/2 of total maximum dose by continuous infusion, with 1/2-2/3 via PCA boluses.) Total morphine dose, continuous infusion plus boluses, above 0.1 mg/kg/hr may occasionally be required but should be used with caution. In most cases, prn analgesic orders are not appropriate. Alternative analgesics including hydromorphone (Dilaudid) 0.015-0.02 mg/kg IV q 3-4 hr may be appropriate in selected cases. Consider use of ketorolac (Toradol) 0.5 mg/kg (30 mg maximum dose) IV q 6-8 hr in addition to opioid analgesia if no contraindication (i.e. gastritis, ulcer, coagulopathy, or renal impairment). Do not use ibuprofen with ketorolac. Repeated doses of meperidine (Demerol) should be avoided because of the risk of seizures.
3. Mild to moderately severe pain - acetaminophen with codeine (1 mg/kg) po q 4 hr.
4. Ibuprofen 10 mg/kg po q 6-8 h if no contraindication (i.e. ketorolac, gastritis, ulcer, coagulopathy, or renal impairment). Limit more frequent dosing to 72 hr maximum duration.
5. Reassess pain control at least twice daily. Analgesics may be weaned as tolerated by decreasing dose, not by prolonging interval between doses.

6. Cefotaxime or cefuroxime 50 mg/kg IV q 8 h if febrile. Substitute clindamycin 10 mg/kg IV q 6 h for known or suspected cephalosporin allergy. Strongly consider adding vancomycin 10-15 mg/kg IV q 8 hr for severe febrile illness or for proven or suspected CNS infection.
7. If applicable, continue prophylactic penicillin. Prophylactic penicillin should be discontinued while patient is receiving broad-spectrum antibiotics.
8. O₂ by nasal cannula or face mask if needed to keep pulse ox $\geq 92\%$ or \geq patient's baseline value (if $> 92\%$). The etiology of a new or increasing supplemental O₂ requirement should be investigated. Avoid excessive or unnecessary O₂, which may suppress the reticulocyte count and exacerbate anemia.
9. Consider transfusion if no evidence of detumescence within 12 hrs:
 - a) Partial exchange or erythrocytapheresis to Hb 10 gm/dl and Hb S (patient's RBC) $\leq 30\%$.
 - b) May consider simple transfusion as alternative to partial exchange transfusion if Hb $< 6-7$ gm/dl (do not transfuse acutely to Hb > 10 gm/dl, hct $> 30\%$).
10. Winter shunt (spongiosum-cavernosum shunt) may be considered if priapism persists for > 24 hrs, unresponsive to supportive care, drainage and irrigation, and transfusions, but is controversial.
11. Observe for severe headache or neurologic signs or symptoms. (Ischemic stroke may occur 1-10 days after onset of priapism, especially following transfusion.)
12. See other Clinical Care Paths for acute chest syndrome, acute splenic sequestration, aplastic crisis, stroke, if present.

DISCHARGE CRITERIA:

1. Priapism resolving (complete detumescence may take 1-2 weeks)
2. Taking adequate oral fluids and able to take po medications (e.g. prophylactic penicillin) if applicable
3. Adequate pain relief on oral analgesics
4. Afebrile ≥ 24 hr. with negative cultures $\geq 24-48$ hr. if applicable.
5. Resolution of any pulmonary symptoms or documentation of adequate oxygenation on room air
6. Consider starting pseudoephedrine 30 mg po hs (< 10 years) or 60 mg po hs (> 10 years) for priapism prophylaxis.
7. Follow up arranged.

GENERAL ANESTHESIA AND SURGERY

General anesthesia is associated with a significant risk for post-operative complications, especially acute chest syndrome. Thus, it should be planned carefully with good communication between the hematologist, anesthesiologist, surgeon, and blood bank. Surgery should only be performed at a center with expertise in sickle cell disease. General principles include:

1. Pre-op evaluation
 - CBC, retic, pulse ox
 - Consider CXR
 - Consider pulmonary function tests for patients with prior history of acute chest syndrome or with suspicion of chronic lung disease.
2. Pre-op transfusion: Simple or partial exchange transfusion should be strongly considered for all members with Hb SS or S β^0 -thalassemia prior to any procedure requiring general anesthesia. Data from a prospective, randomized, multicenter trial suggest that simple transfusion is as efficacious as partial exchange transfusion in most cases. The need for pre-op transfusions must be individualized. Use minor-antigen-matched, sickle-negative, and leukocyte-depleted RBC if available.
 - Simple transfusion : RBC's to increase Hb to 10 gm/dl.
 - Aggressive transfusion: Erythrocytapheresis or serial simple transfusions to decrease Hb S to 30% with Hb approximately 10 gm/dl.

Surgery without pre-op transfusion in members with Hb SS and S β^0 -thalassemia may be considered in selected cases for minor procedures (e.g. PE tubes) with brief anesthetics. Pre-op transfusions may also be appropriate for selected members with Hb SC or S β^+ -thalassemia, especially if they have a history of recurrent acute chest syndrome or evidence of chronic organ damage.

3. Prior to surgery (within 72 h)
 - CBC, retic
 - Consider Hb electrophoresis to document Hb S% (after pre-op transfusions)
 - Hydration (1-1½ x maintenance) ≥12 hr before procedure.
 - Teach incentive spirometry
4. Intraoperative
 - Minimum 50% O₂ with anesthetic agent
 - Avoid hypoxia (continuous pulse ox), hypercarbia, or hyperventilation.
 - Avoid or minimize tourniquets
5. Post-operative
 - O₂ by nasal cannula @ 2L or by face mask @ 35% for 18-24 hr regardless of pulse oximetry.
 - Pulse oximetry for 18-24 hr to ensure supplemental O₂ is sufficient to keep saturation > 95%.
 - IV + PO 1-1½ x maintenance. Avoid excessive hydration, which may precipitate acute chest syndrome.
 - Aggressive pain management.
 - Incentive spirometry - 10 breaths q 2 hr while awake. Encourage early ambulation and activity.

Consider daily CBC, diff, platelet count and reticulocyte count until stable.

CHRONIC TRANSFUSION PROTOCOL

Overview:

Some severe manifestations of sickle cell disease warrant maintenance therapy with chronic blood transfusions. The goal is to suppress erythropoiesis sufficiently and to provide enough normal red blood cells to maintain the percentage of the patient's cells (i.e. hemoglobin S) at less than 30%. Experience has shown that this approach significantly reduces the risk of recurrent stroke. Such transfusions also reduce markedly the incidence of many other sickle-related complications such as vaso-occlusive pain and acute chest syndrome. In addition to preventing acute complications, chronic transfusions may prevent the progression of chronic organ damage and even reverse some pre-existing organ dysfunction. This has been shown most clearly in patients with Hb SS and functional asplenia, some of whom show improved splenic reticuloendothelial function after receiving chronic transfusions. Many members with sickle cell disease treated with chronic transfusions also experience an increased sense of wellbeing, with improved energy levels, exercise tolerance, growth velocity and sexual development. Thus, transfusions to chronically replace sickle cells with normal erythrocytes can be considered a specific therapy that markedly ameliorates the disease.

Indications:

Stroke

Indications in Selected Patients

- Transient ischemic attack
- Abnormal TCD
- Severe or recurrent acute chest syndrome
- Severe debilitating pain
- Following splenic sequestration (as alternative to observation or early surgical splenectomy)
- Recurrent priapism
- Chronic organ failure
- Intractable leg ulcers
- Severe chronic anemia with high output cardiac failure
- Selected pregnancies

Outpatient Transfusions:

PRBC 10-15 ml/kg (minor-antigen-matched, sickle-negative, leukocyte-depleted) given over 3-4 hr with standard monitoring. Minor -antigen matching for Rh (C, D, E,) and Kell should be provided for all patients. More extensive matching should be provided if available, especially for patients with previous alloimmunization. Frequency of transfusions (usually q 3-4 weeks) is adjusted to maintain Hb S \leq 30% (typically with nadir Hb > 9-10 gm/dl). For patients receiving chronic transfusions for stroke who have had no recurrent neurologic events for 3 years, consider decreasing frequency of transfusions to maintain Hb S \leq 50%. Record volume of RBC transfused. Serial erythrocytapheresis is an alternative approach to chronic transfusions that is associated with substantially less or little iron loading and should be seriously considered for patients with adequate venous access. Patients should be immunized to hepatitis A and B. Continue prophylactic penicillin if applicable.

Iron Chelation:

Initiation of chelation with deferasirox (Exjade) should be considered after ≥ 1 year of chronic transfusions and/or serum ferritin is increased to 1500-2000 $\mu\text{g/L}$. Hepatic iron content > 4 mg/gm dry wt liver tissue (as determined by liver biopsy) also has been used as an indication for beginning iron chelation. Initial dose is 20-30 mg/kg/per day, orally, once per day. Use of serial erythrocytapheresis for chronic transfusions may delay or limit the duration or avoid entirely the need for chelation.

Counsel regarding avoidance of excess dietary iron.

Consider vitamin C supplementation, 100-250 mg/d, only at start of each dose of deferoxamine.

Monitoring:

Audiology evaluation if any symptoms present (e.g. tinnitus, difficulty hearing)

Ophthalmology consultation for any new visual symptoms

Prior to each transfusion:

CBC, reticulocyte count, type and cross, antibody screen. Consider serum ferritin and Hb S quantitation

Every 3-6 months

Height, weight, history, physical exam

Hb electrophoresis, ferritin, ALT

Yearly

Liver function tests including ALT. Consider Hepatitis C, HIV, and HTLV I-II serology, calcium, phosphorus, alkaline phosphatase, thyroid profile, fasting glucose, and other endocrine studies as indicated.

Audiology evaluation

Ophthalmology examination

Consider CXR, EKG, echocardiogram

Consider 24 hr urinary iron excretion with 12 hr dose of subcutaneous deferoxamine (usually 40-50 g/kg).

Consider metaphyseal and spinal radiographs.

Consider liver biopsy for histology and quantitative iron.

Consider CNS evaluation including MRI, MRA, and/or neurocognitive testing for patients with stroke

HYDROXYUREA PROTOCOL

Higher levels of fetal hemoglobin (Hb F) and lower leukocyte counts are thought to be beneficial in patients with sickle cell disease and can be achieved with daily oral administration of hydroxyurea (HU). A placebo-controlled, double blind, prospective trial in severely affected adults with Hb SS showed that HU significantly reduced the incidence of vaso-occlusive pain, acute chest syndrome, and blood transfusions. A multi-center phase I/II trial in members > 5 years-of-age showed safety and hematologic effects similar to those observed in adults. Clinical benefit in members with Hb SS has been suggested by a number of open-label trials. The drug is FDA-approved for selected adult patients, with the important caution that the drug is not curative and requires close hematologic monitoring for myelotoxicity and the strict use of contraception by both men and women who are sexually active. Use of HU in patients with Hb SC or β^+ -thalassemia is under investigation.

The clinical course of each patient with sickle cell disease should be regularly reviewed by a pediatric hematologist/sickle cell program and the possibility of hydroxyurea treatment and its pros and cons considered. Many patients with severe complications may also be candidates for either a program of chronic transfusions (p. 27) or, if an HLA-matched sibling is available, stem cell transplantation (p. 29). HU is generally not considered appropriate for patients with stroke, and it is not useful in the treatment of acute sickle pain. No improvement is expected until the drug has been taken daily for 3-6 months. HU may alter the natural history of the sickle cell disease; for example splenomegaly or splenic sequestration may occur in relatively older patients. HU is a potentially toxic chemotherapeutic agent whose long-term toxicity (including concerns about carcinogenicity and teratogenicity) is unresolved. *Thus, the drug should be initiated and monitored only by hematologists with expertise in chemotherapy and sickle cell disease and after written documentation of patient education and consent.*

Indications (Inclusion criteria)

- Dx: Hb SS or S β^0 -thalassemia
- ≥ 3 years-of-age
- ≥ 3 severe vaso-occlusive pain events/year, or
- ≥ 2 episodes of acute chest syndrome/year, or
- Any combination of ≥ 3 episodes of acute chest syndrome and severe pain/year

Exclusion criteria

- Pregnancy
- Inability to use reliable contraception if sexually active (men and women)
- Inability to comply with daily dosing and frequent laboratory monitoring

Dosage

Hydroxyurea 15-30 mg/kg p.o. q.d. (supplied as Droxia [200, 300, and 400mg] and Hydrea [500mg] capsules). All size capsules must be available for accurate dosing. Liquid suspensions, 100mg/ml in flavored syrup, are stable for 1 month and can be prepared for younger members. The dose may be increased by approximately 5 mg/kg/day every 8-12 weeks to a maximum dose of 30 mg/kg/day or until there is evidence of toxicity (see below). Consider folate supplementation, 0.4-1 mg p.o.q.d.

Monitoring

1. CBC, reticulocyte count: baseline, then every 2 weeks until maximum dose tolerated without toxicity for 8-12 weeks; then every 4 weeks.
2. History and physical examination: baseline, then every 4 weeks until maximum dose tolerated for 8-12 weeks, then every 8 weeks. Be alert to the possibility of recurrent or new splenomegaly and risk of splenic sequestration.
 - b. Fractionated bilirubin, ALT, and creatinine: baseline, then every 12-24 weeks.
 - c. Quantitation of hemoglobin F: baseline, every 3 months x 2, then every 6 months.
 - d. Pregnancy test (if menstruating): baseline, then prn. (Stop HU immediately for positive result and offer teratogen risk counseling. Information is available from the Organization of Teratogen Information Services at 888-285-3410 or www.otispregnancy.org).

Toxicity

Toxicity from hydroxyurea is generally defined as any of the following:

ANC < 2000 x 10⁶/L

platelet count < 80,000 x 10⁶/L

absolute reticulocyte count < 80,000 x 10⁶/L if hemoglobin < 9.0 gm/dl

hemoglobin < 5 gm/dl or > 20% below baseline

serum creatinine > 1.0 mg/dl or 50% above baseline

100% increase in ALT

If toxicity occurs, treatment will be stopped for at least 1 week and until toxicity resolves. HU will then be resumed at the same dose or a dose decreased by 2.5-5 mg/kg/d. If toxicity does not recur after 12 wks on the lower dose, the dose may then be increased by 2.5-5 mg/kg/d. If toxicity recurs on the higher dose, then HU will be stopped again until toxicity resolves, and hydroxyurea can then be resumed at the lower dose without further dose escalations.

HEMATOPOIETIC STEM CELL TRANSPLANTATION

Successful allogeneic hematopoietic stem cell transplantation provides a hematologic cure for sickle cell disease. Published experience in children less than 16 years of age shows that about 80% with Hb SS who undergo bone marrow transplantation from an HLA-identical sibling donor will have sustained engraftment and elimination of all sickle-related symptoms. Ten to 15% of patients will reject the stem cell graft, and about 5% will succumb from complications of the procedure. Although not as rigorously studied, the success of transplantation from HLA-identical sibling cord blood or peripheral blood progenitor cells may be similar. There is currently a NIH-funded study to collect cord blood for stem cell transplantation from subsequent siblings of patients with sickle cell disease and other hemoglobinopathies (contact CHORI-Cord Blood Program at 510-450-7605 for further information).

Wide scale implementation of transplantation for sickle cell disease in the United States has been limited by our ability to predict the clinical severity of sickle cell disease for a given member and often by the lack of an HLA-match sibling without sickle cell disease. A consensus of opinion now suggests that allogeneic hematopoietic stem cell transplantation is an appropriate treatment option for patients who have an HLA-identical sibling donor and have experienced a severe clinical course. Such patients include those who have had a stroke or who are experiencing impaired neuropsychologic function with abnormal MRI, recurrent acute chest syndrome, osteonecrosis of multiple joints, and/or recurrent debilitating pain. The procedure should only be undertaken in centers with expertise in both sickle cell disease and transplantation.

Some of the early transplant patients partially rejected donor marrow and became stable mixed chimeras (a mixture of donor and host hematopoiesis) with amelioration of sickle-related symptoms. Non-myeloablative transplant protocols with less intensive and therefore less toxic conditioning regimens are currently under investigation to try to induce stable mixed chimerism in patients with sickle cell disease. Such approaches should decrease the toxicity and cost of transplantation and hopefully achieve clinical benefit. Others are investigating the use of alternative donor or unrelated hematopoietic progenitor cells in severely affected patients without an HLA-identical sibling donor. These approaches are promising, but are currently investigational.

TRANSCRANIAL DOPPLER ULTRASONOGRAPHY

Stroke, defined as an acute, clinically evident neurological event, occurs in 7-11% of patients with Hb SS. Most strokes are ischemic events caused by stenosis or occlusion of large cerebral arteries such as the intracranial internal carotids and middle cerebrals. Stroke typically occurs without warning and causes significant long-term neurologic sequelae in at least 50% of cases. Chronic transfusion after a first stroke reduces markedly the high risk of recurrent stroke, but this is a suboptimal approach because it does not prevent the initial neurologic injury.

Transcranial Doppler (TCD) ultrasonography provides a non-invasive method for identifying members with Hb SS who are at high risk for developing a first stroke. High-risk patients are those with increased blood velocity in large cerebral vessels, indicative of vascular narrowing. Patients with mean blood-flow velocity in the internal carotid or middle cerebral artery of >200cm/second are at highest risk. A prospective randomized study demonstrated that chronic transfusions reduce the risk of first stroke in such high-risk patients. These data have led some to the recommendation of routine TCD screening of members with sickle cell anemia, and the initiation of a chronic transfusion program for those with abnormal screening tests.

Initial transcranial Doppler (TCD) screening should be done between two and three years of age. It should be repeated yearly thereafter.

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